ORIGINAL ARTICLE

Frequency of *De Novo* Hepatocellular Carcinoma after Direct-acting Antiviral Therapy for Chronic Hepatitis C: A Prospective Follow-up

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Abstract

Background: Chronic hepatitis C (CHC) management has changed tremendously after direct-acting antivirals (DAAs) availability. Sustained virological response (SVR) has improved significantly, but one of the major concerns is the chances of *de novo* hepatocellular carcinoma (HCC) development after DAAs. The objective of the study is to calculate the frequency of newly diagnosed cases of HCC after antiviral therapy for CHC in Pakistan.

Materials and methods: This prospective, interventional research was conducted from June 2017 to September 2020. All patients after antiviral therapy for CHC were followed with an ultrasound abdomen and α-fetoprotein, six monthly. Multiphasic computed tomography (CT) of the abdomen was performed in suspected cases. For quantitative variables, the mean and standard deviations were calculated, whereas the qualitative variables were analyzed by frequencies and percentages.

Results: Among 180 patients, 110 were men and 70 were women with a mean age of 45.52 ± 11.71 years. One hundred and twenty-six patients were noncirrhotic, 38 had compensated cirrhosis while 16 had decompensated cirrhosis. One hundred and sixty-four (91.11%) patients achieved SVR, of which 22 (12.22%) patients developed new HCC during follow-up. Compensated cirrhosis group had 10 patients, the decompensated group had 12 patients, and the noncirrhotic group had no new HCC cases. Among patients with the new HCC, 12 achieved SVR.

Conclusion: The risk of the development of HCC after antiviral treatment is highly significant among patients with liver cirrhosis. So, a strict surveillance strategy should be adopted in every cirrhotic patient following treatment with DAA agents even if they achieve SVR.

Clinical significance:

- Chances of developing HCC are still significantly high even after achieving SVR with DAAs in patients with liver cirrhosis.
- Patients with liver cirrhosis should be under surveillance for HCC even after achieving SVR after DAAs treatment.

Keywords: Cirrhosis, Direct acting antiviral, Hepatocellular carcinoma.

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Introduction

Globally, the Hepatitis C virus (HCV) has been considered a chief cause of liver disease that is chronic in nature. According to a survey by the World Health Organization (WHO), the approximate number of people acquiring HCV infection was 185 million. Two-thirds of these HCV-infected patients develop chronic liver disease.[1] Chronic hepatitis C is reported to be highly prevalent across Pakistan. Overall, HCV prevalence is found to be 6.8% with predominant genotype 3, published in a comprehensive review of recent data from a National Survey of Pakistan.[2] Around 20–30% of CHC patients develop cirrhosis if remain untreated. HCC is mostly a serious complication of liver cirrhosis, and annually it may occur at an average rate of 5.7% in patients with liver cirrhosis. Patients with CHC must be more concerned as there is a higher mortality rate of them from cirrhosis and primary HCC.[3] In terms of epidemiology, Pakistan has intermediate epidemicity with an average overall prevalence of HCC to be 3–7% among cirrhotic patients.[4]

Management of HCV infection during the last few years has been undergoing significant changes. DAA agents have been showing high success rates in terms of achieving the SVR in CHC patients.[5,6] Previous literature showed a low risk of developing HCC in patients who achieved the status of SVR. Although more HCV cases have been treated in the past few years after the introduction of DAAs, its prevalence is still high in patients with HCC.[7]

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Several studies conducted worldwide have shown unexpectedly a higher rate of new cases of the HCC (8.1%) among those treated with DAAs during or within 6 months of the completion of treatment.[8,9] Most of these data are from the west. However, data from a few prospective French cohorts found a decreased incidence of newly diagnosed cases of HCC in cirrhotic patients after the achievement of SVR.[10] Kanwal et al. also reported somewhat similar data in cirrhotic patients.[11] These investigations alarmed

the hepatology community and made quite a stir. The purpose of the current research was the determination of new case frequency related to new HCC after DAA treatment in CHC patients.

Materials and Methods

This prospective, interventional quasi-experimental research was conducted in the Department of Gastroenterology and Hepatology, starting from May 2017 to September 2020.

All the patients who were having CHC intervention with or without compensated cirrhosis were followed for at least a year after treatment. Patients with nonalcoholic fatty liver disease, alcoholic liver disease, coinfection with chronic hepatitis B, or prior history of HCC were excluded.

At the time of enrollment, all patients gave written consent, and demographic data were taken. Compensated cirrhosis was defined by the absence of any complications like upper gastrointestinal (GI) bleeding due to portal hypertension, ascites formation, or history of portosystemic encephalopathy in CHC patients, while decompensated cirrhosis was defined by any prior history of upper GI bleeding due to portal hypertension, ascites, or history of portosystemic encephalopathy. After treatment, alpha-fetoprotein (AFP) and ultrasound of the abdomen were done every 6 months during follow-up. Any liver lesion was confirmed by a multiphasic CT scan of the abdomen with contrast. HCC was confirmed based on typical radiological features consistent with HCC. The current research was approved by the Ethical Review Committee of our university.

Statistical Analysis

Data entry and analysis of the patient were done on the 22nd version of SPSS software. For quantitative variables for instance age, the mean and standard deviations of the data were calculated. Whereas the qualitative variables like gender, SVR achieved or not, and presence or absence of HCC were analyzed by their frequencies and percentages.

Results

There were 180 patients enrolled with 110 (61.11%) men and 70 (38.89%) women accounting for a male-to-female ratio of 1.6:1. The mean age was 45.52 ± 11.71 years. According to the severity of the liver disease, 126 (70%) patients were noncirrhotic, 38 (21.1%) were having compensated cirrhosis, and 16 (8.88%) were having decompensated cirrhosis. The mean follow-up after completion of DAA therapy was 15.81 ± 3.02 months (Table 1).

One hundred and sixty-four (91.1%) patients treated with DAAs achieved SVR (Fig. 1) and 22 (12.22%) patients out of 180 DAA-exposed patients developed *de novo* HCC during the follow-up period (Fig. 2).

Stratification of new HCC cases with respect to gender, age, the severity of the disease, and SVR achieved is shown in (Table 2). There were 18 (81%) men of which 15 (68.18%) were above the age of 45 years. Compensated cirrhosis group comprised 10 patients, 12 patients were in the decompensated group, and none were in the noncirrhotic group. SVR was achieved in 12 patients of which 22 were with new-onset HCC.

Table 1: Baseline characteristics of the study population

Factors	*Results n(%)*
Gender	
Male	110 (61.11%)
Female	70 (38.89%)
Age	
<45 yrs	92 (51.11%)
>45 yrs	88 (48.89%)
Severity of the disease	
CHC, noncirrhotic	126 (70%)
Compensated cirrhotic	38 (21%)
Decompensated cirrhotic	16 (8.88%)

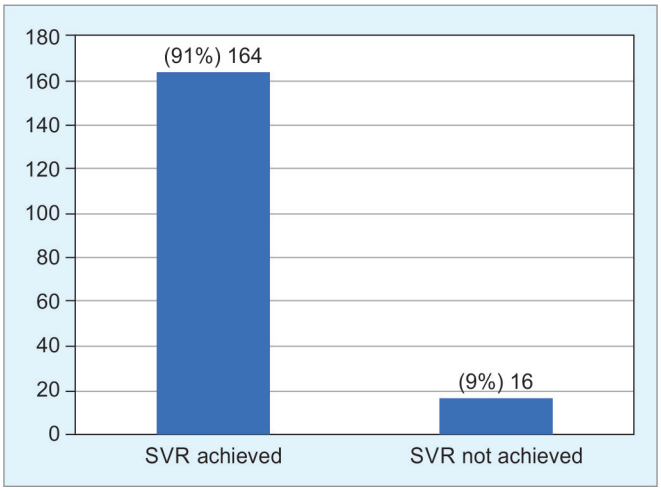

Fig. 1: Frequency of patients achieving SVR after direct acting antiviral therapy

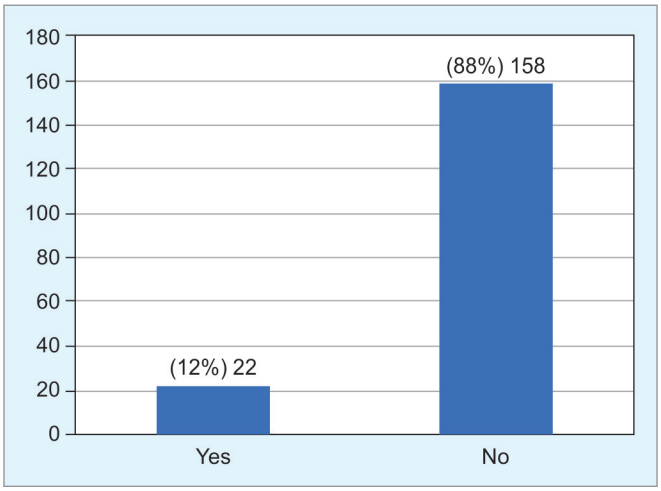

Fig. 2: Frequency of *de novo* cases of the HCC after the completion of direct acting antiviral therapy in the CHC patients ($n = 180$)

Discussion

Interventions that are being used for CHC have evolved during the last decade with the introduction of DAA therapy. Excellent treatment response achieved by DAAs is attributed to good patient compliance, low side-effect profile, and easy oral administration. In our study, nearly 91% of patients achieved SVR, which is comparable to previously reported national and international data.

Previous data on the use of DAA demonstrated the fact that achievement of SVR after treatment with DAAs results in a reduction

Table 2: Associated characteristics of *de novo* cases of HCC after direct acting antiviral therapy ($n = 22$)

Factors	*De novo HCC cases n(%)*
Severity of disease	
Noncirrhotic	0
Compensated cirrhosis	10 (45.45%)
Decompensated cirrhosis	12 (54.5%)
Gender	
Male	18 (81%)
Female	4 (18.1%)
SVR	
Achieved	12 (54.54%)
Not achieved	10 (45.45%)
Age pattern	
<45 yrs	7 (31.81%)
>45 yrs	15 (68.18%)

of risk of complications, which also include the HCC development.[12] Meta-analysis of 12 research studies regarding interferon (IFN)-based treatment of CHC also demonstrated a strong relation between SVR achievement and reduction of the risk of development of HCC with a significantly high number of around 76%.[13–15]

However, some international literature regarding DAA has suggested an increased risk of recurrence of previously treated HCC and even newly diagnosed cases of HCC undergoing treatment intervention of DAA in CHC patients despite achieving the SVR.[16] In our research, 22 patients during the follow-up time developed HCC of which 12 achieved SVR, which is quite a significant number.

Debes et al. suggested the possible mechanism of carcinogenesis after DAA treatment, implementing the role of high levels of a few of the inflammatory cytokines, named [interleukin (IL)-21, IL-22, IL-3, monokine induced by gamma (MIG), a proliferation-inducing ligand (APRIL), tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), vascular endothelial growth factor (VEGF), and stem cell factor (SCF)] in the development of new HCC cases after DAA treatment.[17] Another study by Faillaci et al. demonstrated that an increase in VEGF levels caused by DAA therapy is the main culprit for carcinogenesis, specifically in susceptible individuals with abnormal activation of neoangiogenetic pathways in liver tissue.[18]

Conti et al. in the multicenter study on cirrhotic patients treated with 24 weeks of DAA reported new HCC cases (3.2%) and also HCC recurrence (28.8%) in previously treated HCC.[3] Previous history of HCC and child class was found to be independent factors while no correlation was found between newly developed HCC cases and HCV genotype and the type of DAA regimen used. In our study, the prevalence of HCC is quite high (12.22%) as compared to Conti et al., but we have a longer follow-up and historically we have more contribution of genotype 3 in Pakistan. Few other smaller single-center uncontrolled studies demonstrated similar results, but their median follow-up time was small and mainly these were retrospective studies. So, no definite conclusions could be made.

Multiple large cohort studies have also demonstrated similar results. According to data from the USA, 271 new HCC cases were diagnosed out of 22,500 patients received DAA. Among 271 HCC cases, 183 achieved SVR after treatment with DAAs.[11] The risk of having HCC was seen to be higher in patients with cirrhosis than in noncirrhotic. Data from our study supported the findings of the above study, demonstrating a significant number of patients who were in the cirrhotic group developing *de novo* HCC, even after the achievement of SVR. Another important finding of our study is a very high number of HCC, i.e., 10 out of 38 in patients with compensated cirrhosis, which is against the natural history of the disease. Historically, HCC occurs after decompensated cirrhosis in CHC patients. It was rarely seen in compensated cirrhosis. The number of newly diagnosed HCC cases after DAA therapy in the patients with compensated cirrhosis in current research study is alarming.

Limitations were certainly present in the current study including being a single-center study with a small sample size. Furthermore, the impact of a different regimen of antiviral drugs may have different effects on carcinogenesis, which needs to further elaboration.

Conclusion

The authors concluded that the risk of development of HCC after interventional DAA treatment is still significantly high in compensated and decompensated cirrhotic patients, even after achieving SVR. So, a strict surveillance strategy should be adopted in all cirrhotic patients after treatment with DAA agents.

Clinical Perspectives

- SVR has been significantly improved with DAAs for the treatment of CHC patients.
- Now, patients with advanced liver diseases like decompensated liver cirrhosis may be treated effectively with DAAs.
- Chances of developing HCC are still significantly high even after achieving SVR with DAAs in patients with liver cirrhosis.
- Patients with liver cirrhosis should be under surveillance for HCC even after achieving SVR after DAAs treatment.

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